SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

CHEMICAL CATEGORY NAME

Quat category

SPONSORED CHEMICALS

SUBCATEGORY I: AMINOETHYL ACRYLATES

Dimethylaminoethyl acrylate methyl chloride	**CASRN 44992-01-0**
Dimethylaminoethyl acrylate dimethyl sulfate	**CASRN 13106-44-0**

SUBCATEGORY II: AMINOETHYL METHACRYLATES

Dimethylaminoethyl methacrylate methyl chloride	**CASRN 5039-78-1**
Dimethylaminoethyl methacrylate dimethyl sulfate	**CASRN 6891-44-7**

SUPPORTING CHEMICALS

Dimethylaminoethyl acrylate	**CASRN 2439-35-2**
Dimethylaminoethyl methacrylate	**CASRN 2867-47-2**

The High Production Volume (HPV) Challenge Program[1] was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance[2,3] and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT's focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT may not develop HCs for those HPV chemicals which have recently been assessed and published internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments. HCs may be created if new data suggest a need to update the case work where the OECD document will be used as key support documentation.

[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

Chemical Abstract Service Registry Number (CASRN)	**Subcategory I** **Sponsored Chemicals** **44992-01-0** **13106-44-0** **Subcategory II** **Sponsored Chemicals** **5039-78-1** **6891-44-7** **Supporting Chemicals** **2439-35-2** **2867-47-2**
Chemical Abstract Index Name	**Subcategory I** **Sponsored Chemicals** **Ethanaminium, N,N,N-trimethyl-2-[(1-oxo-2-propenyl)oxy]-, chloride (1:1)** **Ethanaminium, N,N,N-trimethyl-2-[(1-oxo-2-propenyl)oxy]-, methyl sulfate (1:1)** **Subcategory II** **Sponsored Chemicals** **Ethanaminium, N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propenyl)oxy]-, chloride (1:1)** **Ethanaminium, N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propenyl)oxy]-, methyl sulfate (1:1)** **Supporting Chemicals** **2-Propenoic acid, 2-(dimethylamino)ethyl ester** **2-Propenoic acid, 2-methyl-, 2-(dimethylamino)ethyl ester**
Structural Formula	**See Appendix**

Summary

The quat category consists of 4 quaternary ammonium salts of the esters of acrylic and methacrylic acid, dimethylaminoethyl acrylate and dimethylaminoethyl methacrylate. These substances are solids possessing negligible vapor pressure and tend to be dispersible in water. The substances contained in the quat category are expected to possess high mobility in soil. Volatilization is expected to be low since these are ionic substances. Hydrolysis is expected to be negligible. The rate of atmospheric photooxidation is moderate. Members of the quat category are expected to possess low persistence (P1) and low bioaccumulation potential (B1).

Human Health Hazard

Structural differences between acrylate and methacrylate compounds may result in different toxicological responses. For this reason, the quat category has been divided into two subcategories to assess human health hazards. Each subcategory includes an analog chemical with data that is used to read-across to sponsored members.

Subcategory I: Aminoethyl acrylates

Acute oral toxicity is low (CASRN 44992-01-0; ADAMMC, sponsored chemical); acute dermal toxicity is moderate, and acute inhalation toxicity is high in rats (CASRN 2439-35-2; ADAM, supporting chemical) for members of this subcategory. A 13-week repeated-dose toxicity study with the supporting chemical, dimethylaminoethyl acrylate (CASRN 2439-35-2; ADAM), showed lung effects (hemorrhage, edema and congestion) and significant increases in the incidence and severity of forestomach lesions (infiltration of inflammatory cells, hyperplasia/ hyperkeratosis, ulceration and necrosis) in rats gavaged at 50 mg/kg-day; the NOAEL for systemic toxicity is 10 mg/kg-day. A combined repeated-dose/reproductive/developmental toxicity screening test with this same supporting chemical showed increased mortality and histopathology (ulceration, hyperplasia of the forestomach and an infiltration of inflammatory cells in the forestomach and lymph nodes) in rats gavaged at 100 mg/kg-day; the NOAEL for systemic and maternal toxicity is 20 mg/kg-day. No effects on reproductive (fertility index, gestation length, parturition, number of corpora lutea/implantation sites) or developmental parameters (litter size, sex ratio, pup weight, viability index) were observed in this study; the NOAEL for reproductive and developmental toxicity is 100 mg/kg-day (highest dose tested). A prenatal developmental toxicity screening test with the same chemical showed increased mortality in treated dams and developmental effects (impaired skeletal ossification) following gavage administration at $\geq$ 30 mg/kg-day; the NOAEL for maternal/developmental toxicity is 10 mg/kg-day. The sponsored chemical, dimethylaminoethyl acrylate methyl chloride (CASRN 4492-01-0; ADAMMC) was not mutagenic in bacterial or mammalian cells and did not induce chromosomal aberrations *in vitro*. The supporting chemical, ADAM, did not induce micronuclei *in vivo*. The sponsored chemical, ADAMMC, is not irritating to rabbit skin; however, it is irritating to rabbit eyes and sensitizing to guinea pig skin.

Subcategory II: Aminoethyl methacrylates

The acute oral and dermal toxicities in rats are low for members of this subcategory. In a 28-day oral repeated-dose toxicity study in rats, the sponsored chemical, dimethylaminoethyl methacrylate methyl chloride (CASRN 5039-78-1; MADAMMC), showed no significant treatment effects at 1000 mg/kg-day, other than decreased body weight gain; the NOAEL for

systemic toxicity is 1000 mg/kg-day (highest dose tested). A combined repeated-dose/reproductive/developmental toxicity screening test with the supporting chemical, dimethylaminoethyl methacrylate (CASRN 2867-47-2; MADAM), showed decreased body weight gain, histopathology (degeneration of nerve fibers in the brain and spinal cord; an infiltration of inflammatory cells in forestomach mucosa), thymic atrophy and organ weight changes following gavage administration at 1000 mg/kg-day; the NOAEL for systemic toxicity is 200 mg/kg-day. This study also showed significant reproductive (total litter loss), developmental (decreased pup weight and viability index) and maternal effects (decreased body weight gain, mortality) at 1000 mg/kg-day; the NOAEL for reproductive/developmental/maternal toxicity is 200 mg/kg-day. The sponsored chemical, MADAMMC, was not mutagenic in bacterial or mammalian cells and did not induce chromosomal aberrations *in vitro*. The supporting chemical, MADAM, did not induce micronuclei *in vivo*. This substance is corrosive to rabbit skin and eyes and irritating, but not sensitizing to guinea pig skin.

Hazard to the Environment

The fish 96-hr LC_{50} for the quat category ranges from 75 mg/L (dimethylaminoethyl acrylate methyl chloride) to >100 mg/L (for the remaining category members); the 48-hr EC_{50} for aquatic invertebrates is >100 mg/L. The 72-hr EC_{50} (growth) for aquatic plants ranges from 0.65 mg/L (dimethylaminoethyl acrylate methyl chloride) to >100 mg/L (dimethylaminoethyl methacrylate methyl chloride) for the quat category.

No data gaps were identified under the HPV Challenge Program.

The sponsor, the Quat HPV Challenge Task Group, submitted a Test Plan and Robust Summaries to EPA for the quat (quaternary ammonium salts) category on April 27, 2004. EPA posted the submission on the Chem RTK HPV Challenge website on May 13, 2004 (http://www.epa.gov/oppt/chemrtk/pubs/summaries/quatcatg/c15210tc.htm). EPA comments on the original submission were posted to the website on August 24, 2005. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on December 21, 2006, which were posted to the Chem RTK website on January 19, 2007.

Category Justification

The quat category consists of the following substances:

Sponsored chemicals

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate methyl chloride (ADAMMC)	CASRN 44992-01-0
Dimethylaminoethyl acrylate dimethyl sulfate (ADAMDMS)	CASRN 13106-44-0

Subcategory II: Aminoethyl methacrylates

Dimethylaminoethyl methacrylate methyl chloride (MADAMMC)	CASRN 5039-78-1
Dimethylaminoethyl methacrylate dimethyl sulfate (MADAMDMS)	CASRN 6891-44-7

Supporting chemicals

Dimethylaminoethyl acrylate (ADAM)	CASRN 2439-35-2
Dimethylaminoethyl methacrylate(MADAM)	CASRN 2867-47-2

Category Justification

The sponsor proposed grouping the quaternary ammonium salts of acrylic and methacrylic acid esters in the quat category based on similarities in chemical structure and physical-chemical properties. EPA considers the justification for this category to be appropriate; however, acrylates and methacrylates exhibit structural differences that may impact biological activity. For this reason, the quat category has been divided into two subcategories. Subcategory I includes the sponsored chemicals, dimethylaminoethyl acrylate methyl chloride (ADAMMC) and dimethylaminoethyl acrylate dimethyl sulfate (ADAMDMS). Subcategory II includes the sponsored chemicals, dimethylaminoethyl methacrylate methyl chloride (MADAMMC) and dimethylaminoethyl methacrylate dimethyl sulfate (MADAMDMS). For the purposes of human health hazard characterization, a read-across approach is supported within (but not between) subcategories. For ecotoxicity purposes, the supporting chemicals are not necessary to fill the ecological endpoints.

Justification for Supporting Chemical

The sponsor proposed use of two supporting chemicals, dimethylaminoethyl acrylate (ADAM) and dimethylaminoethyl methacrylate (MADAM) as data sources to address human health endpoints for the quat category based on shared structural and toxicological properties. These compounds have been tested extensively, with IUCLID and SIDS documents available for both:

(SIDS Dossier ID 2439-35-2, http://www.chem.unep.ch/irptc/sids/OECDSIDS/2439352.pdf; SIDS Dossier ID 2867-47-2, http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIMETHYLAMINO.pdf). Despite deficiencies in the sponsor's analog justification, EPA considers the use of these supporting chemicals to be appropriate, as they represent a conservative approach for human health hazard characterization; however, due to the lack of repeated-dose toxicity studies for the sponsored chemicals which would facilitate comparisons, and the expected differences in mechanisms of action that may impact toxicological responses (to acrylate and methacrylate moieties), the mammalian toxicity data for ADAM should only be used to address hazards that may be associated with members of subcategory I. Similarly, the mammalian toxicity data for MADAM should only be used to address subcategory II.

1. Chemical Identity

1.1 Identification and Purity

The following information was taken from the 2006 Test Plan:
Quaternized ammonium salts are manufactured via derivatization of the corresponding tertiary amine with methyl chloride or dimethyl sulfate in a closed system to produce the quaternary amine. Briefly, the ester precursor is formed by reacting dimethylaminoethanol with acrylic or methacrylic acid, thereby producing dimethylaminoethyl acrylate (ADAM) or dimethylaminoethyl methacrylate (MADAM). These esters differ by a single methyl group on the acrylic chain. Because the tertiary amine is caustic and unstable, it is reacted with methyl chloride or dimethyl sulfate to produce a more stable and less caustic quaternary amine salt. For this reason, ADAM and MADAM have a methyl chloride salt (ADAMMC and MADAMMC) and a dimethyl sulfate salt (ADAMDMS and MADAMDMS). The purity of these substances where indicated, is high (99.9%).

1.2 Physical-Chemical Properties

The physical-chemical properties for members of the quat category are provided in Table 1; the environmental fate properties are provided in Table 2. These substances are solids possessing negligible vapor pressure and tend to be dispersible in water.

Table 1. Physical Chemical Properties of Quat Category[1]

Property	Ethanaminium, N,N,N-trimethyl-2-[(1-oxo-2-propen-1-yl)oxy]-, chloride (1:1)	Ethanaminium, N,N,N-trimethyl-2-[(1-oxo-2-propen-1-yl)oxy]-, methyl sulfate (1:1)	Ethanaminium, N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propen-1-yl)oxy]-, chloride (1:1)	Ethanaminium, N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propen-1-yl)oxy]-, methyl sulfate (1:1)
CASRN	44992-01-0	13106-44-0	5039-78-1	6891-44-7
Molecular Weight	193.7	269.3	207.7	283.3
Physical State[5]	Solid	Solid	Solid	Solid
Melting Point	>25 °C (solid)	>25 °C (solid)	>25 °C (solid)	>25 °C (solid)
Boiling Point	>300 °C	>300 °C	>300 °C	>300 °C

	(estimated)[2]; Most quaternary ammonium compounds decompose before boiling[3]	(estimated)[2]; Most quaternary ammonium compounds decompose before boiling[3]	(estimated)[2]; Most quaternary ammonium compounds decompose before boiling[3]	(estimated)[2]; Most quaternary ammonium compounds decompose before boiling[3]
Vapor Pressure	5.3×10^{-7} mm Hg at 25 °C (estimated)[2]	$<1.0 \times 10^{-10}$ mm Hg at 25 °C (estimated)[2]	3.0×10^{-7} mm Hg at 25 °C (estimated)[2]	$<1.0 \times 10^{-10}$ mm Hg at 25 °C (estimated)[2]
Dissociation Constant (pK_a)	Not applicable			
Henry's Law Constant	$<1.0 \times 10^{-10}$ atm-m^3/mole (estimated)[2]	$<1.0 \times 10^{-10}$ atm-m^3/mole (estimated)[2]	$<1.0 \times 10^{-10}$ atm-m^3/mole (estimated)[2]	$<1.0 \times 10^{-10}$ atm-m^3/mole (estimated)[2]
Water Solubility	Dispersible[3]	Dispersible[3]	Dispersible[3]	Dispersible[3]
Log K_{ow}	Not applicable due to dispersibility[4]	Not applicable due to dispersibility[4]	Not applicable due to dispersibility[4]	Not applicable due to dispersibility[4]

[1] Quat HPV Challenge Group Revised Test Plan and Robust Summary for Quat Category. November 16, 2006. Available at: http://www.epa.gov/chemrtk/pubs/summaries/quatcatg/c15210tc.htm as of July 29, 2011
[2] U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of July 29, 2011.
[3] Dery M. Kirk-Othmer Encycolpedia of Chemical Technology. Quaternary Ammonium Compounds. December 4, 2000.
[4] Tolls, J., Sijm, D. 2000. Estimating properties of surface active chemical. In: Handbook of Property Estimation for Chemicals. Boethling, R. S., Mackay, D. (eds.). Lewis Publishers, Boca Raton, FL. pp 419–446.
[5] The commercial products are manufactured and shipped as an aqueous solution (75-80%).

2. General Information on Exposure

2.1 Production Volume and Use Pattern

The quat category chemicals had an aggregated production and/or import volume in the United States between 51 million pounds and 111 million pounds during calendar year 2005.

- CASRN 44992-01-0: 50 million to < 100 million pounds;
- CASRN 13106-44-0: < 500,000 pounds;
- CASRN 5039-78-1: 1 million to < 10 million pounds;
- CASRN 6891-44-7: < 500,000 pounds;

CASRN 44992-01-0:
Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other basic organic chemical manufacturing as "other." No commercial and consumer uses were reported for the chemical.

CASRN 13106-44-0:
Non-confidential information in the IUR indicated that the industrial processing and uses, and commercial and consumer uses of the chemical are not readily obtainable (NRO).

CASRN 5039-78-1:
Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other basic organic chemical manufacturing as "other." Non-confidential commercial and consumer uses of the chemical include "other."

CASRN 6891-44-7:
No industrial processing and uses, and commercial and consumer uses were reported for the chemical.

2.2 Environmental Exposure and Fate

The environmental fate properties of the quat category members are provided in Table 2. Members of the quat category possess high mobility in soil. Ethanaminium, N,N,N-trimethyl-2-[(1-oxo-2-propen-1-yl)oxy]-, chloride (1:1) (CASRN 44992-01-0) was degraded 86.5% (14 days), 84.8% (14 days) and 82.7 (27 days) when tested at 60, 150 and 300 mg/L, respectively using the Zahn-Wellens (OECD 302A) test and was classified as inherently biodegradable. Ethanaminium, N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propen-1-yl)oxy]-, chloride (1:1) was degraded 69% after 28 days as measured by CO_2 evolution using the modified Sturm (OECD 301B) test and was classified as readily biodegradable. Volatilization of the substances contained within the quat category is low since they are ionic compounds. The rate of hydrolysis is negligible and the rate of atmospheric photooxidation is expected to be moderate for all compounds in this category. Members of the quat category are expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 2. Physical Chemical Properties of Quat Category[1]				
Property	Ethanaminium, N,N,N-trimethyl-2-[(1-oxo-2-propen-1-yl)oxy]-, chloride (1:1)	Ethanaminium, N,N,N-trimethyl-2-[(1-oxo-2-propen-1-yl)oxy]-, methyl sulfate (1:1)	Ethanaminium, N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propen-1-yl)oxy]-, chloride (1:1)	Ethanaminium, N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propen-1-yl)oxy]-, methyl sulfate (1:1)
CASRN	44992-01-0	13106-44-0	5039-78-1	6891-44-7
Photodegradation Half-life	5.0 hours (estimated)[2]	5.0 hours (estimated)[2]	3.7 hours (estimated)[2]	3.7 hours (estimated)[2]
Hydrolysis Half-life	329 days at pH 8 (estimated)[2]; 9 years at pH 7 (estimated)[2]	329 days at pH 8 (estimated)[2]; 9 years at pH 7 (estimated)[2]	6.8 years at pH 8 (estimated)[2]; 68 years at pH 7 (estimated)[2]	6.8 years at pH 8 (estimated)[2]; 68 years at pH 7 (estimated)[2]
Biodegradation	82.7 – 96.5% after 27 days (inherently biodegradable)	No data	69% after 28 days (readily biodegradable)	No data
Bioaccumulation Factor	BAF = 0.9 (estimated)[2]	BAF = 0.9 (estimated)[2]	BAF = 0.9 (estimated)[2]	BAF = 0.9 (estimated)[2]
Log K_{oc}	1.2 (estimated)[2]	1.1 (estimated)[2]	1.4 (estimated)[2]	1.0 (estimated)[2]
Fugacity (Level III Model)[2]				
Air (%)	<0.1	<0.1	<0.1	<0.1
Water (%)	28.4	33.9	25.9	35.0
Soil (%)	71.5	66.0	74.1	64.9
Sediment (%)	<0.1	0.1	<0.1	0.1
Persistence[3]	P1 (low)	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation[3]	B1 (low)	B1 (low)	B1 (low)	B1 (low)

[1] Quat HPV Challenge Group Revised Test Plan and Robust Summary for Quat Category. Available at: http://www.epa.gov/chemrtk/pubs/summaries/quatcatg/c15210tc.htm as of July 29, 2011

[2] U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of July 29, 2011.

[3] Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: The quat category consists of 4 quaternary ammonium salts of the esters of acrylic and methacrylic acid, dimethylaminoethyl acrylate and dimethylaminoethyl methacrylate. These substances are solids possessing negligible vapor pressure and tend to be dispersible in water. The substances contained in the quat category are expected to possess high mobility in soil. Volatilization is expected to be low since these are ionic substances. Hydrolysis is expected to be negligible. The rate of atmospheric photooxidation is moderate. Members of the quat category are expected to possess low persistence (P1) and low bioaccumulation potential (B1).

3. Human Health Hazard

A summary of health effects data submitted for SIDS endpoints is provided in Table 3. The table also indicates where data for tested category members are read-across (RA) to untested members of the category as appropriate.

Acute Oral Toxicity

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate methyl chloride (CASRN 44992-01-0)
(1) Sprague-Dawley rats (5/sex/dose) were administered CASRN 44992-01-0 (as an 80% aqueous solution in 0.5% methylcellulose) via the oral route at 500, 900, 1600, 2000 or 2900 mg/kg in males and 900, 1600 or 2000 mg/kg in females. The animals were observed for 15 days following dosing. Mortality occurred at 1600 mg/kg (40%) and 2000 mg/kg (100%).
LD_{50} = 1600 – 1800 mg/kg

(2) Sprague-Dawley rats (2/sex/dose) received CASRN 44992-01-0 (as an 80% aqueous solution) via gavage administration at 25, 200, 2000 or 5000 mg/kg and were observed for 5 days following dosing, or until signs of toxicity subsided. Mortality was observed at 2000 mg/kg, (50%) and at 5000 mg/kg (100%). In a second study, Sprague-Dawley rats (5/sex) were gavaged at 200 mg/kg and observed for 5 days following dosing, or until signs of toxicity subsided. No mortality was observed at this dose.
$LD_{50} \geq$ 2000 mg/kg

Subcategory II: Aminoethyl methacrylates

Dimethylaminoethyl methacrylate methyl chloride (CASRN 5039-78-1)
Sprague-Dawley rats received CASRN 5039-78-1 (as a 78% aqueous solution) via gavage administration at 1000 (five males) or 2000 mg/kg (five/sex) and observed for 14 days following dosing. One rat died at 2000 mg/kg.
LD_{50} > 2000 mg/kg

Acute Dermal Toxicity

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate (CASRN 2439-35-2, supporting chemical)
Sprague-Dawley rats (5/sex/dose) were administered CASRN 2439-35-2 via the dermal route at 200, 330, 500, 700, 980, 1400 or 2000 mg/kg under semi-occluded conditions for 24 hours and observed for 15 days following dosing. Mortality occurred at all doses tested except 200 mg/kg (males). See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/2439352.pdf
LD_{50} = 419 mg/kg

Subcategory II: Aminoethyl methacrylates

Dimethylaminoethyl methacrylate (CASRN 2867-47-2, supporting chemical)
Sprague-Dawley rats (10/sex) were administered CASRN 2867-47-2 via the dermal route at 2000 mg/kg for 24 hours and observed for 72 hours following exposure. No mortalities occurred. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIMETHYLAMINO.pdf
LD_{50} > 2000 mg/kg

Acute Inhalation Toxicity

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate (CASRN 2439-35-2, supporting chemical)

Sprague-Dawley rats (5/sex/dose) were exposed whole-body to CASRN 2439-35-2 as an aerosol at 0, 0.04, 0.06, 0.09 or 0.46 mg/L for 4 hours and observed for 14 days following dosing. Mortality occurred at all concentrations tested in males and at the two highest concentrations in females. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/2439352.pdf
LC_{50} = 0.07 mg/L

Repeated-Dose Toxicity

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate (CASRN 2439-35-2, supporting chemical)
(1) In a combined repeated-dose reproductive/developmental toxicity screening test, Sprague-Dawley rats (12/sex/dose) were administered CASRN 2439-35-2 (99.9% purity) in corn oil via gavage administration at 0, 4, 20 or 100 mg/kg-bw-day. Males were dosed for 43 days; females were dosed 14 days prior to mating through day 3 of lactation. Two mortalities (females) occurred at 100 mg/kg-day. Males treated at 100 mg/kg-day showed decreased body weight gain and food consumption; thickening of forestomach mucosa and enlarged pancreatic-duodenal lymph nodes were observed in both sexes. Histopathological findings at 100 mg/kg-day include ulceration, inflammatory cell infiltration, hyperplasia of forestomach mucosa and leukocyte infiltration in the pancreatic-duodenal lymph nodes in both sexes. Hematological changes (i.e., increased reticulocyte, platelet and segmented neutrophil counts and decreased albumin levels) were limited to males treated at 100 mg/kg-day; decreased absolute thymus weight was observed in females treated at 100 mg/kg-day. Similar histopathological changes were observed in the forestomach of males treated at 20 mg/kg-day; atrophy of the thymus was observed in females treated at 20 mg/kg-day. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/2439352.pdf
LOAEL = 100 mg/kg-day (based on mortality and histopathology findings)
NOAEL = 20 mg/kg-day

(2) In a 90-day repeated-dose toxicity study, Sprague-Dawley rats were administered CASRN 2439-35-2 (99.9% purity) in peanut oil via gavage administration at 0, 2, 10 or 50 mg/kg-day. The four treatment groups contained 20, 10, 10, and 25 rats/sex, respectively. Clinical signs of toxicity (respiratory distress, ptyalism) and extensive mortality (22 rats) were observed at 50 mg/kg-day. In some cases, mortality was attributed to lung lesions caused by aspiration of regurgitated stomach contents. An increase in neutrophil counts (both sexes) and a decrease in lymphocyte counts (males only) was observed at 50 mg/kg-day. Pathological findings include grayish foci in forestomach mucosa, enlarged pancreatic lymph nodes and dilation and/or reddish discoloration in the lungs. No changes in hematology or pathology were noted at the end of the recovery period. Microscopic examination of decedents and survivors after 13 weeks of exposure revealed forestomach lesions (infiltration of inflammatory cells, ulceration, hyperplasia/hyperkeratosis, granulation, edema and necrosis) and hemorrhage or edema/congestion in the lungs at 50 mg/kg-day in both sexes. Lung effects may be associated with dosing errors; therefore the level of confidence for this finding is low. Similar effects (i.e., hyperplasia/hyperkeratosis, edema and an infiltration of inflammatory cells) were seen in the forestomach of males (4/10) treated at 10 mg/kg-day; however, these findings were less severe (minimal grade). See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/2439352.pdf
LOAEL = 50 mg/kg-day (based on mortality, forestomach lesions and lung effects)
NOAEL = 10 mg/kg-day

Subcategory II: Aminoethyl methacrylates

Dimethylaminoethyl methacrylate methyl chloride (CASRN 5039-78-1)
In a 28 day repeated dose study, Sprague-Dawley rats were administered CASRN 5039-78-1 (as a 75-78% aqueous solution) by oral gavage at 0 or 500 mg/kg-day (10/sex), 50 or 150 mg/kg-day (5/sex) and 0 or 1000 mg/kg-day (10/sex) for 28 days. No mortality occurred. Significant decreases in food consumption and body weight gain occurred in males and females at 1000 mg/kg-day as compared to controls. No significant effects were observed in urinalysis, hematology, blood chemistry, organ weight or pathology evaluations.
NOAEL = 1000 mg/kg-day (highest dose tested)

Dimethylaminoethyl methacrylate (CASRN 2867-47-2, supporting chemical)
In a combined repeated-dose/reproductive/developmental toxicity screening test, Sprague-Dawley rats (12/sex/group) were administered CASRN 2867-47-2 (99.9% purity) in corn oil by gavage at 0, 40, 200 or 1000 mg/kg-day for 43 days (males) or 41-52 days (i.e., from 2 weeks prior to mating though day 3 of lactation in females). Mortality (3 females) occurred at 1000 mg/kg-day. Other treatment-related effects observed at 1000 mg/kg-day include: clinical signs of toxicity (twitching, chronic convulsions in both sexes), decreased body weight gain (both sexes) and histopathological changes (degeneration of nerve fibers in the brain and spinal cord, infiltration of inflammatory cells in forestomach in both sexes and thymic atrophy in females). Increased organ weight of liver (male), adrenal (female) and kidney (both sexes) was also observed at 1000 mg/kg-day (in the absence of histopathological changes). Hematological effects (decreased erythrocyte, hemoglobin and hematocrit levels) were observed in males at concentrations $\geq$ 200 mg/kg-day. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIMETHYLAMINO.pdf

LOAEL = 1000 mg/kg-day (based on decreased body weight gain, histopathology and organ weight changes)
NOAEL = 200 mg/kg-day

Reproductive Toxicity

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate (CASRN 2439-35-2, supporting chemical)
In the combined repeated-dose reproductive/developmental toxicity screening test in Sprague-Dawley rats described previously, dams were administered CASRN 2439-35-2 by oral gavage at 0, 4, 20 or 100 mg/kg-day. No significant treatment-related effects on reproductive (fertility, number of corpora lutea/implantation sites, gestation length, parturition) or developmental parameters (litter size, sex ratio, pup weight, viability index) were observed. Similarly, an examination of external features, clinical signs and necropsy results showed no adverse effects in offspring born to treated dams at any dose tested. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/2439352.pdf
NOAEL (reproductive/developmental toxicity) = 100 mg/kg-day (highest dose tested)

Subcategory II: Aminoethyl methacrylates

Dimethylaminoethyl methacrylate (CASRN 2867-47-2, supporting chemical)
In the combined repeated-dose reproductive/developmental toxicity screening test described previously, three dams treated at 1000 mg/kg-day lost all of their pups during lactation. No other treatment-related effects on reproductive parameters (e.g., mating/fertility index, numbers of corpora lutea or implantation sites, gestation length or parturition) were observed. Mortality, clinical signs of toxicity (twitching, chronic convulsions), decreased body weight gain, histopathology (degeneration of nerve fibers in the brain and spinal cord, infiltration of inflammatory cells in forestomach and thymic atrophy) and organ weight changes (increased kidney and adrenal weights) were observed in dams treated at 1000 mg/kg-day. Offspring born to dams treated at 1000 mg/kg-day exhibited significant decreases in body weight ($p < 0.05$) and a low viability index. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIMETHYLAMINO.pdf
LOAEL (reproductive toxicity) = 1000 mg/kg-day (based on increased litter loss)
NOAEL (reproductive toxicity) = 200 mg/kg-day
LOAEL (maternal toxicity) = 1000 mg/kg-day (based on mortality)
NOAEL (maternal toxicity) = 200 mg/kg-day
LOAEL (developmental toxicity) = 1000 mg/kg-day (decreased body weight/viability index)
NOAEL (developmental toxicity) = 200 mg/kg-day

Developmental Toxicity

In a prenatal developmental toxicity screening test, pregnant Sprague-Dawley rats (25 dams/dose group) were administered CASRN 2439-35-2 (in peanut oil) via gavage administration at 0, 10, 30 or 100 mg/kg-day for two weeks after mating (i.e., gestation days 6-15). Mortality and clinical signs of toxicity (respiratory distress, piloerection, chromorhinorrhea, hunched posture

and dyspnea) occurred at ≥ 30 mg/kg-day. Macroscopic pathological findings include gaseous dilatation and thickening of mucosa in the gastrointestinal tract in animals treated at ≥ 30 mg/kg-day. Other effects observed in treated dams include respiratory difficulty, reduced food consumption and decreased body weight gain at 100 mg/kg-day. Treatment-related effects on developmental parameters include an increase in post-implantation loss (including early and late resorptions) and a decrease in fetal body weight at 100 mg/kg-day. In addition, external (dwarfism, adactyly) and internal (cleft palate, hydrocephaly, testicular ectopia and reduced or absent skeletal ossification) developmental anomalies occurred in offspring born to dams treated at 100 mg/kg-day. Impaired ossification of cranial and vertebral sites was observed in affected offspring at 30 mg/kg-day. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/2439352.pdf
LOAEL (maternal toxicity) = 30 mg/kg-day (based on mortality)
NOAEL (maternal toxicity) = 10 mg/kg-day
LOAEL (developmental toxicity) = 30 mg/kg-day (based on impaired skeletal ossification)
NOAEL = 10 mg/kg-day

Genetic Toxicity – Gene Mutation

In vitro

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate methyl chloride (CASRN 44992-01-0)
(1) *Salmonella typhimurium* (*S. typhimurium*) strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to CASRN 44992-01-0 (80% in aqueous solution) at 0, 100, 500, 1000, 2000 or 5000 µg/plate with and without metabolic activation. The ratio of revertants in treated versus control plates never exceeded 1.6. Positive and negative controls were included and responded appropriately. Cell viability data was not provided. No significant increase in mutation frequency was observed.
CASRN 44992-01-0 was not mutagenic in this assay.

(2) Mouse lymphoma ($T/K^{+/-}$) L5178Y cells were exposed to CASRN 44992-01-0 at 0, 30, 100, 300, 1000 or 2000 µg/mL with and without metabolic activation for 4 hours. Positive and negative controls were included and responded appropriately. No precipitation was observed; however, the highest concentration tested (2000 µg/mL) was cytotoxic. No significant increase in mutant frequency was observed.
CASRN 4492-01-0 was not mutagenic in this assay.

Subcategory II: Aminoethyl methacrylates

Dimethylaminoethyl methacrylate methyl chloride (CASRN 5039-78-1)
(1) *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to CASRN 5039-78-1 (75% aqueous solution) at 0, 313, 625, 1250, 2500 or 5000 mg/plate with and without metabolic activation. A positive control was included and responded appropriately. The ratio of revertants in treated versus control plates never exceeded 1.4. There was no

significant increase in mutation frequency either in the presence or absence of metabolic activation.
CASRN 5039-78-1 was not mutagenic in this assay.

(2) Mouse lymphoma ($T/K^{+/-}$) L5178Y cells were exposed to CASRN 5039-78-1 (75% aqueous solution) at 0, 1250, 2500, 3750 or 5000 µg/mL with and without metabolic activation for 4 hours. Positive controls were included and responded appropriately. Cell viability ranged from 54 – 91% without metabolic activation and 41-77% with metabolic activation. No precipitation of test article was observed. No increase in mutant colonies was observed either in the presence or absence of metabolic activation.
CASRN 5039-78-1 was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate methyl chloride (CASRN 44992-01-0)
Human lymphocytes were exposed to CASRN 44992-01-0 at 0, 156, 625 and 1250 µg/mL in the absence of metabolic activation and 0, 313, 1250, 2000 or 3000 µg/mL in the presence of metabolic activation. Positive and negative controls were included and responded appropriately. An increase (2.5%) of aberrant cells was observed at the highest dose; however, this value was within the control range and therefore was not considered to be indicative of clastogenic activity. No treatment-related effect was seen with metabolic activation. Information regarding cytotoxicity was not provided.
CASRN 44992-01-0 did not induce chromosomal aberrations in this assay.

Subcategory II: Aminoethyl methacrylates

Dimethylaminoethyl methacrylate methyl chloride (CASRN 5039-78-1)
Human lymphocytes were exposed to CASRN 5039-78-1 (75% aqueous solution) at 0, 625, 1250, 2500 or 5000 µg/mL for 2 hours of a 24 hour incubation with and without metabolic activation. Positive and negative controls were included and responded appropriately. No significant increase in chromosomal damage was seen at any dose tested with or without metabolic activation. Information regarding toxicity was not provided.
CASRN 5039-78-1 did not induce chromosomal aberrations in this assay.

In vivo

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate (CASRN 2439-35-2, supporting chemical)
Swiss OF1/CO:OF1(IOPS Caw) mice (5/sex/group and one additional group of 3 mice/sex) were administered CASRN 2439-35-2 via intraperitoneal injection at 75 mg/kg-bw. Two injections were administered 24 hours apart. Two animals were found dead 48 hours after the second

injection. Animals were sacrificed 24 and 48 hours after the second administration of test article and bone marrow smears were examined for the presence of micronuclei in 2000 polychromatic erythrocytes per mouse and for the PCE/NCE ratio. Positive and negative controls were included and responded appropriately. Two mortalities were observed 48 hours after the second injection (these animals were replaced with supplementary ones). A decrease in the P/N ratio was observed indicating that the test material reached the bone marrow, but the number of micronucleated polychromatic cells in the dosed animals was not significantly different from that seen in controls. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/2439352.pdf
CASRN 2439-35-2 did not induce micronuclei in this assay.

Subcategory II: Aminoethyl methacrylates

Dimethylaminoethyl methacrylate (CASRN 2867-47-2, supporting chemical)
(1) NMRI mice (5/sex/group) received CASRN 2867-47-2 as a single gavage administration at 1000 mg/kg-bw. Positive and negative controls were included and responded appropriately. Bone marrow smears were prepared 24, 48 and 72 hours after test article administration and examined for the presence of micronuclei in 1000 polychromatic erythrocytes (PCE) per mouse. No significant increase in the number of micronucleated polychromatic cells was observed in treated versus control animals. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIMETHYLAMINO.pdf
CASRN 2867-47-2 did not induce micronuclei in this assay.

(2) Swiss OF1/CO:OF1 IFFA–CREDO mice (5/sex and one additional group of 3 /sex) were exposed to CASRN 2867-47-2 via intraperitoneal injection at 200 mg/kg-bw. Two injections were administered 24 hours apart. Bone marrow smears were prepared 24 and 48 hours after test article administration and examined for the presence of micronucleated polychromatic erythrocytes in 2000 polychromatic erythrocytes per mouse and the ratio of PCE/NCE. Negative and positive controls were included and responded appropriately. No significant differences in the mean values of micronucleated polychromatic erythrocytes were observed when compared to controls. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIMETHYLAMINO.pdf
CASRN 2867-47-2 did not induce micronuclei in this assay.

Additional Information

Skin Irritation

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate methyl chloride (CASRN 44992-01-0)
Three New Zealand White rabbits received CASRN 44992-01-0 (as an 80% aqueous solution) via dermal application (0.5 mL) to intact, clipped skin under semi-occlusive conditions for 4 hours. Treated areas were scored (according to the Draize scale) at 24, 48 and 72 hours post-exposure. No erythema or edema was observed.
CASRN 44992-01-0 was not irritating to rabbit skin in this assay.

Subcategory II: Aminomethyl methacrylates

Dimethylaminoethyl methacrylate (CASRN 2867-47-2, supporting chemical)
(1) Four rabbits were exposed to undiluted CASRN 2867-47-2 (0.5 mL) via topical application to intact and abraded skin under occlusive conditions for 24 hours and observed 24 and 72 hours following application. Treatment-related effects included severe erythema, edema and necrosis at the site of application to intact and abraded skin. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIMETHYLAMINO.pdf
CASRN 2867-47-2 was corrosive to rabbit skin in this assay.

(2) Rabbits were exposed to CASRN 2867-47-2 via dermal administration under unspecified conditions. The test material was highly irritating to rabbit skin. No additional information was provided. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIMETHYLAMINO.pdf
CASRN 2867-47-2 was highly irritating to rabbit skin in this assay.

(3) Guinea pigs were exposed to CASRN 2867-47-2 via dermal administration under unspecified conditions. The test material was highly irritating to guinea pig skin. No additional information was provided. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIMETHYLAMINO.pdf
CASRN 2867-47-2 was highly irritating to guinea pig skin in this assay.

Eye Irritation

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate methyl chloride (CASRN 44992-01-0)
A volume of 0.1 ml of CASRN 44992-01-0 was instilled in the right eye of a single New Zealand White rabbit for 1 second and effects were observed at 1 and 24 hours afterwards. A dulling of the normal luster of the cornea was observed one hour after treatment and diffuse corneal opacity was observed at 24 hours following the application. Moderate irritation with diffuse beefy red discoloration of the conjunctivae accompanied by severe swelling and extensive discharge was observed at 1 hour after treatment. Similar effects were observed at 24 hours, including diffuse corneal opacity and areas of hemorrhage and necrosis over the conjunctivae and nictitating membranes.
CASRN 44992-01-0 was irritating to rabbit eyes in this assay.

Dimethylaminoethyl acrylate (CASRN 2439-35-2, supporting chemical)
Two New Zealand White rabbits received CASRN 2439-35-2 (0.1 mL) via intraocular administration. Test article was instilled in the right eye and eyelids were held together for one second before rinsing with 20 mL of lukewarm water approximately four seconds after instillation. Marked corneal, iris and conjunctival lesions were apparent within 1 hour of treatment.
CASRN 2439-35-2 was corrosive to rabbit eyes in this assay.

Subcategory II: Aminomethyl methacrylates

Dimethylaminoethyl methacrylate (CASRN 2867-47-2, supporting chemical)
Two rabbits (strain not specified) received CASRN 2867-47-2 (0.1 mL) via intraocular administration in the right eye; the left eye served as control. Eye lids were held together for one second before rinsing with 20 mL of lukewarm water approximately4 seconds after instillation. Treatment-related effects (severe corneal, iridial and conjunctival lesions) were observed two hours after instillation.
CASRN 2867-47-2 was corrosive to rabbit eyes in this assay.

Sensitization

Subcategory I: Aminoethyl acrylates

Dimethylaminoethyl acrylate methyl chloride (CASRN 44992-01-0)
Twenty guinea pigs (sex/strain not specified) were induced with aqueous CASRN 44992-01-0 during a guinea pig maximization test. Animals were exposed to the test article in three stages (i.e., intradermal induction, topical induction and a challenge). In the intradermal induction phase, animals received a dermal injection (0.1 mL) of diluted CASRN 44992-01-0 (1% aqueous solution) with Freund's adjuvant on Day 0. On Day 7, animals were subjected to the topical induction phase which involved dermal administration of CASRN 44992-01-0 (25% aqueous solution) to shaved skin for 48 hours under occlusive conditions. During the challenge phase of the study (Day 21), animals received undiluted CASRN 44992-01-0 via dermal administration to clipped, intact skin under occlusive conditions for 24 hours. Test sites were scored 24 days after the initial intradermal induction phase. No reactions were observed in solvent controls; however, CASRN 44992-01-0 was a strong sensitizer under the conditions of this assay. Additional details are available in TSCATS (OTS0555905).
CASRN 44992-01-0 was sensitizing to guinea pig skin in this assay.

Subcategory II: Aminoethyl methacrylates

Dimethylaminoethyl methacrylate (CASRN 2867-47-2, supporting chemical)
Dunkin Hartley guinea pigs (5/sex in control and 10/sex in treated group) were administered CASRN 2867-47-2 in three stages (intradermal induction, topical induction and a challenge). The intradermal induction on day 1 consisted of a dermal injection (0.1 mL) of CASRN 2867-47-2 (1% in an isotonic solution of 0.9% NaCl) with Freund's adjuvant. On day 8, 0.5 mL of the test substance (at a concentration of 25%) was administered via topical application to the skin. Animals then went 12 days without treatment before a challenge test. This involved re-administration via topical application of 0.5 mL of the test article (at a concentration of 5%) to the left flank and topical administration of the test vehicle on the right flank. Both substances were held in place for 24 hours using an occlusive dressing. Skin reactions were very slight; those observed at the 24-hour time interval were resolved after 48 hours. See human health data at:
http://www.chem.unep.ch/irptc/sids/OECDSIDS/DIMETHYLAMINO.pdf
CASRN 2867-47-2 was not sensitizing in this assay.

Conclusion:

Subcategory I: Aminoethyl acrylates

Acute oral toxicity is low (CASRN 44992-01-0; ADAMMC, sponsored chemical); acute dermal toxicity is moderate and acute inhalation toxicity is high in rats (CASRN 2439-35-2; ADAM, supporting chemical) for members of this subcategory. A 13-week repeated-dose toxicity study with the supporting chemical, dimethylaminoethyl acrylate (CASRN 2439-35-2; ADAM), showed lung effects (hemorrhage, edema and congestion) and significant increases in the incidence and severity of forestomach lesions (infiltration of inflammatory cells, hyperplasia/ hyperkeratosis, ulceration and necrosis) in rats gavaged at 50 mg/kg-day; the NOAEL for systemic toxicity is 10 mg/kg-day. A combined repeated-dose/reproductive/developmental toxicity screening test with this same supporting chemical showed increased mortality and histopathology (ulceration, hyperplasia of the forestomach and an infiltration of inflammatory cells in the forestomach and lymph nodes) in rats gavaged at 100 mg/kg-day; the NOAEL for systemic and maternal toxicity is 20 mg/kg-day. No effects on reproductive (fertility index, gestation length, parturition, number of corpora lutea/implantation sites) or developmental parameters (litter size, sex ratio, pup weight, viability index) were observed in this study; the NOAEL for reproductive and developmental toxicity is 100 mg/kg-day (highest dose tested). A prenatal developmental toxicity screening test with the same chemical showed increased mortality in treated dams and developmental effects (impaired skeletal ossification) following gavage administration at ≥ 30 mg/kg-day; the NOAEL for maternal/developmental toxicity is 10 mg/kg-day. The sponsored chemical, dimethylaminoethyl acrylate methyl chloride (CASRN 4492-01-0; ADAMMC) was not mutagenic in bacterial or mammalian cells and did not induce chromosomal aberrations *in vitro*. The supporting chemical, ADAM, did not induce micronuclei *in vivo*. The sponsored chemical, ADAMMC, is not irritating to rabbit skin; however, it is irritating to rabbit eyes and sensitizing to guinea pig skin.

Subcategory II: Aminoethyl methacrylates

The acute oral and dermal toxicities in rats are low for members of this subcategory. In a 28-day oral repeated-dose toxicity study in rats, the sponsored chemical, dimethylaminoethyl methacrylate methyl chloride (CASRN 5039-78-1; MADAMMC), showed no significant treatment effects at 1000 mg/kg-day, other than decreased body weight gain; the NOAEL for systemic toxicity is 1000 mg/kg-day (highest dose tested). A combined repeated-dose/reproductive/developmental toxicity screening test with the supporting chemical, dimethylaminoethyl methacrylate (CASRN 2867-47-2; MADAM), showed decreased body weight gain, histopathology (degeneration of nerve fibers in the brain and spinal cord; an infiltration of inflammatory cells in forestomach mucosa), thymic atrophy and organ weight changes following gavage administration at 1000 mg/kg-day; the NOAEL for systemic toxicity is 200 mg/kg-day. This study also showed significant reproductive (total litter loss), developmental (decreased pup weight and viability index) and maternal effects (decreased body weight gain, mortality) at 1000 mg/kg-day; the NOAEL for reproductive/developmental/maternal toxicity is 200 mg/kg-day. The sponsored chemical, MADAMMC, was not mutagenic in bacterial or mammalian cells and did not induce chromosomal aberrations *in vitro*. The supporting chemical, MADAM, did not induce micronuclei *in vivo*. This substance is corrosive to rabbit skin and eyes and irritating, but not sensitizing to guinea pig skin.

Table 3. Summary of Human Health Data						
	Subcategory I			**Subcategory II**		
Endpoints	**SPONSORED CHEMICAL Dimethylamino-ethyl acrylate dimethyl sulfate (13106-44-0)**	**SPONSORED CHEMICAL Dimethylamino-ethyl acrylate methyl chloride (44992-01-0)**	**SUPPORTING CHEMICAL Dimethylamino-ethyl acrylate (2439-35-2)**	**SPONSORED CHEMICAL Dimethylamino ethyl methacrylate dimethyl sulfate (6891-44-7)**	**SPONSORED CHEMICAL Dimethylamino-ethyl methacrylate methyl chloride (5039-78-1)**	**SUPPORTING CHEMICAL Dimethylamino-ethyl methacrylate (2867-47-2)**
Acute Oral Toxicity LD_{50} (mg/kg)	No Data 1600-1800 (RA)	**1600 - 1800**	–	No Data > 2000 (RA)	**> 2000**	–
Acute Inhalation Toxicity LC_{50} (mg/L)	No Data 0.07 (RA)	No Data 0.07 (RA)	**0.07**	–	–	–
Acute Dermal Toxicity LD_{50} (mg/kg)	No Data 419 (RA)	No Data 419 (RA)	**419**	No Data > 2000 (RA)	No Data > 2000 (RA)	**> 2000**
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-day)	No Data NOAEL = 10 LOAEL = 50 (RA)	No Data NOAEL = 10 LOAEL = 50 (RA)	**NOAEL = 10 LOAEL = 50**	No Data NOAEL = 1000 (hdt) (RA)	**NOAEL = 1000 (hdt)**	**NOAEL = 200 LOAEL = 1000**
Reproductive Toxicity NOAEL/LOAEL (mg/kg-day) **Reproductive Toxicity**	No Data NOAEL = 100 (hdt) (RA)	No Data NOAEL = 100 (hdt) (RA)	**NOAEL = 100 (hdt)**	No Data NOAEL = 200 LOAEL = 1000 (RA)	No Data NOAEL = 200 LOAEL = 1000 (RA)	**NOAEL = 200 LOAEL = 1000**

Table 3. Summary of Human Health Data						
	Subcategory I			**Subcategory II**		
Endpoints	**SPONSORED CHEMICAL Dimethylamino-ethyl acrylate dimethyl sulfate (13106-44-0)**	**SPONSORED CHEMICAL Dimethylamino-ethyl acrylate methyl chloride (44992-01-0)**	**SUPPORTING CHEMICAL Dimethylamino-ethyl acrylate (2439-35-2)**	**SPONSORED CHEMICAL Dimethylamino ethyl methacrylate dimethyl sulfate (6891-44-7)**	**SPONSORED CHEMICAL Dimethylamino-ethyl methacrylate methyl chloride (5039-78-1)**	**SUPPORTING CHEMICAL Dimethylamino-ethyl methacrylate (2867-47-2)**
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-day)						
Maternal and Developmental Toxicity	No Data NOAEL = 10 LOAEL = 30 (RA)	No Data NOAEL = 10 LOAEL = 30 (RA)	**NOAEL = 10** **LOAEL = 30**	No Data NOAEL = 200 LOAEL= 1000 (RA)	No Data NOAEL = 200 LOAEL= 1000 (RA)	**NOAEL = 200** **LOAEL= 1000**
Genetic Toxicity – Gene Mutation ***In vitro***	No Data Negative (RA)	**Negative**	–	No Data Negative (RA)	**Negative**	–
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	No Data Negative (RA)	**Negative**	–	No Data Negative (RA)	**Negative**	–
Genetic Toxicity-Chromosomal Aberrations ***In vivo***	No Data Negative (RA)	No Data Negative (RA)	**Negative**	No Data Negative (RA)	No Data Negative (RA)	**Negative**
Additional Information	No Data			No Data	No Data	
Skin Irritation		**Not irritating**	–			**Corrosive**
Eye Irritation		**irritating**	–			**Corrosive**
Sensitization		**Sensitizing**	–			**Not sensitizing**

Measured data in bold text; (RA) = Read Across; (hdt) = highest dose tested; (–) indicates that endpoint was not addressed for this chemical

4. Environmental Effects – Aquatic Toxicity

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 2.

Acute Toxicity to Fish

***Dimethylaminoethyl methacrylate dimethyl sulfate* (CASRN 6891-44-7)**
Zebra fish (*Brachydanio rerio*) were exposed to dimethylaminoethyl methacrylate dimethyl sulfate (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 96 hours. No analytical monitoring was conducted. No mortalities were observed.
96-h LC_{50} > 100 mg/L

***Dimethylamino ethylacrylate dimethyl sulfate* (CASRN 13106-44-0)**
Zebra fish (*Brachydanio rerio*) were exposed to dimethylaminoethyl acrylate dimethyl sulfate (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 96 hours. No mortalities were observed.
96-h LC_{50} > 100 mg/L

***Dimethylaminoethyl methacrylate methyl chloride* (CASRN 5039-78-1)**
Zebra fish (*Brachydanio rerio*) were exposed to dimethylaminoethyl methacrylate methyl chloride (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 96 hours. No analytical monitoring was conducted. No mortalities were observed.
96-h LC_{50} > 100 mg/L

***Dimethylaminoethyl acrylate methyl chloride* (CASRN 44992-01-0)**
(1) Zebra fish (*Brachydanio rerio*) were exposed to dimethylaminoethyl acrylate methyl chloride (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 96 hours. No analytical monitoring was conducted. No mortalities were observed.
96-h LC_{50} > 100 mg/L

(2) Zebra fish (*Brachydanio rerio*) were exposed to dimethylaminoethyl acrylate methyl chloride (80% solution in water) at nominal concentrations of 50, 100, 150, 200, 250 or 300 mg/L under static conditions for 96 hours. No analytical monitoring was conducted. Deviations with respect to oxygen saturation (3% below required value) occurred during testing. Mortalities were observed at 100 mg/L. Mortality was 100% at concentrations > 100 mg/L.
96-h LC_{50} = 75 mg/L

Acute Toxicity to Aquatic Invertebrates

***Dimethylaminoethyl methacrylate dimethyl sulfate* (CASRN 6891-44-7)**
Water fleas (*Daphnia magna*) were exposed to dimethylaminoethyl methacrylate dimethyl sulfate (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 48 hours. No analytical monitoring was conducted. *D. magna* immobilization was not observed.
48-h EC_{50} > 100 mg/L

***Dimethylaminoethyl acrylate dimethyl sulfate* (CASRN 13106-44-0)**
Water fleas (*Daphnia magna*) were exposed to dimethylaminoethyl acrylate dimethyl sulfate (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 48 hours. No analytical monitoring was conducted. *D. magna* immobilization was not observed.
48-h EC_{50} > 100 mg/L

***Dimethylaminoethyl methacrylate methyl chloride* (CASRN 5039-78-1)**
Water fleas (*Daphnia magna*) were exposed to dimethylaminoethyl methacrylate methyl chloride (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 48 hours. No analytical monitoring was conducted. Immobility of 5% of the daphnid population was observed for the lowest two concentrations.
48-h EC_{50} > 100 mg/L

***Dimethylaminoethylacrylate methyl chloride* (CASRN 44992-01-0)**
(1) Water fleas (*Daphnia magna*) were exposed to dimethylaminoethyl acrylate methyl chloride (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 48 hours. No analytical monitoring was conducted. Immobility of 5% of the daphnid population was observed for the lowest two concentrations.
48-h EC_{50} > 100 mg/L

(2) Water fleas (*Daphnia magna*) were exposed to dimethylaminoethyl acrylate methyl chloride (80% solution in water) at nominal concentrations of 0, 5, 10, 20, 40, 80, 160 or 320 mg/L under static conditions for 48 hours. No analytical monitoring was conducted. 100% immobilization was observed at the concentration of 320 mg/L.
48-h EC_{50} = 120 mg/L

Toxicity to Aquatic Plants

***Dimethylaminoethyl methacrylate dimethyl sulfate* (CASRN 6891-44-7)**
Green algae (*Scenedesmus subspicatus*) were exposed to dimethylaminoethyl methacrylate dimethyl sulfate (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 72 hours. No analytical monitoring was conducted. Algal concentrations were measured after 24, 48 and 72 hours. Algae exposed to 1, 10 and 100 mg/L responded with 7, 21 and 60% growth inhibition, respectively.
72-h EC_{50} (growth) = 10 – 100 mg/L

***Dimethylaminoethyl acrylate dimethyl sulfate* (CASRN 13106-44-0)**
Green algae (*Scenedesmus subspicatus*) were exposed to dimethylaminoethyl acrylate dimethyl sulfate (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 72 hours. No analytical monitoring was conducted.
72-h EC_{50} (growth) = 10 – 100 mg/L
***Dimethylaminoethyl methacrylate methyl chloride* (CASRN 5039-78-1)**
Green algae (*Scenedesmus subspicatus*) were exposed to dimethylaminoethyl methacrylate methyl chloride (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 72 hours. No analytical monitoring was conducted. Algae exposed to 10 or 100 mg/L responded with 2 or 26% growth inhibition, respectively.

72-h EC_{50} (growth) > 100 mg/L

Dimethylaminoethyl acrylate methyl chloride **(CASRN 44992-01-0)**
(1) Green algae (*Scenedesmus subspicatus*) were exposed to dimethylaminoethylacrylate methyl chloride (80% solution in water) at nominal concentrations of 0, 1, 10 or 100 mg/L under static conditions for 72 hours. No analytical monitoring was conducted. Growth inhibition was 11% at 1 mg/L, 79% at 10 mg/L and 98% at 100 mg/L.
72-h EC_{50} (growth) = 1 – 10 mg/L

(2) Green algae (*Scenedesmus subspicatus*) were exposed to dimethylaminoethyl acrylate methyl chloride at nominal concentrations of 0, 5, 10, 20, 40, 80, 160 or 320 mg/L under static conditions. Growth occurred in the control group and no other, so the test was stopped. *Scenedesmus subspicatus* were then exposed to dimethylaminoethylacrylate methyl chloride (80% solution in water) at nominal concentrations of 0.1, 0.2, 0.4, 0.8, 1.6, 3.2 or 6.4 mg/L. No analytical monitoring was conducted. Each concentration and controls were inoculated with ~10,000 algae/mL. The extinction of an aliquot of the test vessels was measured photometrically.
72-h EC_{50} (growth) = 0.65 mg/L

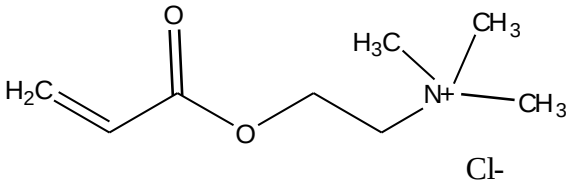
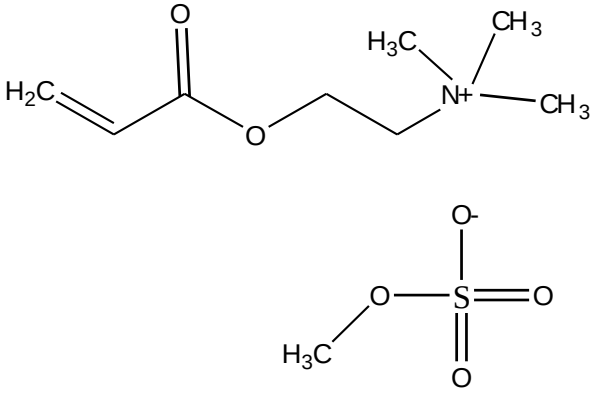
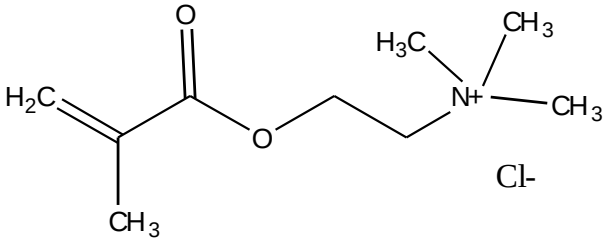
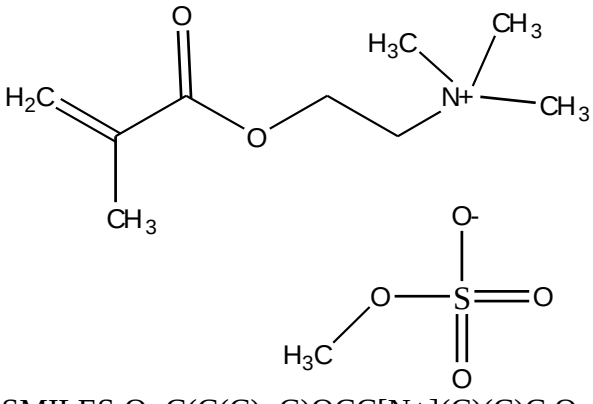
Conclusion: The fish 96-hr LC_{50} for the quat category ranges from 75 mg/L (dimethylaminoethyl acrylate methyl chloride) to >100 mg/L (for the remaining category members); the 48-hr EC_{50} for aquatic invertebrates is >100 mg/L. The 72-hr EC_{50} (growth) for aquatic plants ranges from 0.65 mg/L (dimethylaminoethyl acrylate methyl chloride) to >100 mg/L (dimethylaminoethyl methacrylate methyl chloride) for the quat category.

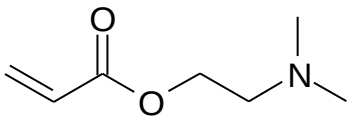
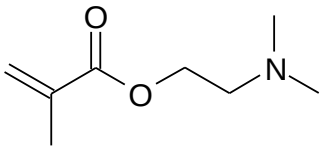
Table 2. Summary of Environmental Effects – Aquatic Toxicity Data

Endpoints	SPONSORED CHEMICAL Dimethylaminoethyl acrylate dimethyl sulfate (13106-44-0)	SPONSORED CHEMICAL Dimethylaminoethyl acrylate methyl chloride (44992-01-0)	SPONSORED CHEMICAL Dimethylaminoethyl methacrylate dimethyl sulfate (6891-44-7)	SPONSORED CHEMICAL Dimethylaminoethyl methacrylate methyl chloride (5039-78-1)
Fish 96-h LC_{50} (mg/L)	**> 100**	**75**	**> 100**	**> 100**
Aquatic Invertebrates 48-h EC_{50} (mg/L)	**> 100**	**> 100**	**> 100**	**> 100**
Aquatic Plants 72-h EC_{50} (mg/L)	**10 – 100**	**0.65**	**10 – 100**	**> 100**

Bold = experimental data (i.e., derived from testing)

APPENDIX

Chemical Name	CASRN	Structure
Sponsored Chemicals		
Ethanaminium, N,N,N-trimethyl-2-[(1-oxo-2-propen-1-yl)oxy]-, chloride (1:1)	44992-01-0	 SMILES: O=C(C=C)OCC[N+](C)(C)C.[Cl-]
Ethanaminium, N,N,N-trimethyl-2-[(1-oxo-2-propen-1-yl)oxy]-, methyl sulfate (1:1)	13106-44-0	 SMILES: O=C(C=C)OCC[N+](C)(C)C.O=S(OC)([O-])=O
Ethanaminium, N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propen-1-yl)oxy]-, chloride (1:1)	5039-78-1	 SMILES: O=C(C(C)=C)OCC[N+](C)(C)C.[Cl-]
Ethanaminium, N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propen-1-yl)oxy]-, methyl sulfate (1:1)	6891-44-7	 SMILES:O=C(C(C)=C)OCC[N+](C)(C)C.O=S(OC)([O-)=O

Supporting Chemicals		
2-Propenoic acid, 2-(dimethylamino) ethyl ester	2439-35-2	 SMILES: C(C(OCCN(C)C)=O)=C
2-Propenoic acid, 2-methyl-,2-(dimethylamino) ethyl ester	2867-47-2	 SMILES: C(C(OCCN(C)C)=O)(=C)C